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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,861	04/25/2001	Daniel Dupret	58763.000013	4902

7590 03/03/2004

Robert M. Schulman, Esq.
Hunton & Williams
Suite 1200
1900 K Street, N.W.
Washington, DC 20006

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,861	DUPRET ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,37-41 and 50-92* is/are pending in the application.

4a) Of the above claim(s) *37-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,37-41 and 50-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action responds the Amendment received on January 20, 2004.

Preliminary Remark

The Office acknowledges the cancellation of claims 2-36 and 42-49, and addition of new claims 50-92.

On page 8 of the Applicants' response, Applicants indicate that claims 1 and 50-92 are now pending. Applicants are advised that claims 37-39, while withdrawn for being drawn to a non-elected invention, non-elected without traverse, are still pending.

Therefore, claims 1, 37-41, and 50-92 are pending, but claims 1 and 50-92 are currently under prosecution.

Election/Restrictions

This application contains claims 37-39 drawn to an invention nonelected without traverse in the response received on December 24, 2002. Cancellation is required.

Priority

Applicants' foreign priority claim is acknowledged.

Claim Objections

The objection of claims 10-13, 22, 23, 27, 28, 29, 31, 33-35, and 43 for being in improper claim format, made in the Office Action mailed on July 30, 2003 is withdrawn in view of the Amendment received on January 20, 2004, canceling the objected claims.

Claim Rejections - 35 USC § 112

The rejection of claims 22, 23, 25, 30, and 36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on July 30, 2003 is withdrawn in view of the Amendment received on January 20, 2004, canceling the rejected claims.

New Rejections – Necessitated by Amendment

The present rejection is necessitated by the newly filed claims, submitted in the Amendment received on January 20, 2004

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51, 52, 68, 72, and 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51 is indefinite for the recitation of the phrase, "until at least a majority of the hybridized fragments have immediately adjacent ends," because it is unclear what is present at the immediately adjacent ends of the fragments. For the purpose of prosecution, the phrase is interpreted as the majority of the hybridized fragments having a fragment that is immediately adjacent thereto.

Claim 52 is indefinite for the recitation of the phrase, "all of the hybridized fragments have immediately adjacent ends," because it is unclear what is present at the immediately

adjacent ends of the fragments. For the purpose of prosecution, the phrase is interpreted as all of the hybridized fragments having a fragment that is immediately adjacent thereto.

Claim 68 is indefinite for the recitation of the phrase, "the ligase is a thermostable ligase that is active at ***high*** temperature," because it is unclear what range of temperature is considered to be "high," rendering the claim indefinite in its metes and bounds as to at what temperature (or range of temperatures) a ligase is considered to be thermostable. It appears that the term, "thermostable' is an art-recognized term and therefore, the deletion of the phrase, "that is active at high temperature" would better characterize the invention.

Claim 72 is indefinite for the recitation of the term, "novel," as the term is an evolving term, rendering the metes and bounds of the claim indefinite.

Claim 91 is indefinite for the recitation of the term, "single-stranded exonuclease," as an exonuclease is an enzyme and neither single- or double-stranded. Amending the claim to recite, "exonuclease which cleaves single stranded nucleic acids," would overcome this rejection.

Claim Rejections - 35 USC § 102

The rejection of claims 1-18, 20-36, 42-44, and 49 under 35 U.S.C. 102(b) as being anticipated by Stemmer et al. (PNAS, 1994, vol. 91, pages 10747-10751; IDS ref#63), made in the Office Action mailed on July 30, 2003 is withdrawn in view of the Amendment received on January 20, 2004, amending the claims to require the use of a ligase for the recombination method.

Claim Rejections - 35 USC § 103

The rejection of claims 45-48 under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (PNAS, vol. 91, pages 10747-10751; IDS ref#63) in view of Rouwendal et al. (Biotechniques, 1993, vol.15, no. 1, pages 68-70 and 72-75), made in the Office Action mailed on July 20, 2003 is withdrawn in view of the Amendment received on January 20, 2004.

The rejection of claim 19 under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (PNAS, vol. 91, pages 10747-10751; IDS ref#63) in view of Gary et al. (The Journal of Biological Chemistry, 1997, vol. 272, no. 39, pages 24522-24529), made in the Office Action mailed on July 20, 2003 is withdrawn in view of the Amendment received on January 20, 2004.

Double Patenting – Necessitated by Amendment

The instant rejection is necessitated by the Amendment received on January 20, 2004, amending the claims to become drawn to a ligase-mediated recombination reaction.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 50-61, 65-90, and 92 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 81-83, 85, 86, 88-102, and 105 of copending Application No. 09/723,316. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1 and 50 of the instant application are obvious in view of claim 81 of 09/723,316 application, hereto referred to as the '316 application because both claims are drawn to a ligase-mediated recombination via use of oligonucleotide fragments derived from two heterologous polynucleotide sequences of a polynucleotide bank (or library), followed by hybridization of the fragments to an assembly matrix, further followed by ligation of the two adjacent oligonucleotide fragments hybridized onto said assembly matrix. While claim 81 of the '316 patent differs from instant claim 1, the difference is not patentably distinct because the nature of the method is drawn to emulating molecular evolution, requiring iterations of the steps. This is further evidenced by instant claim 50, which recites that the method is at least once repeated.

Instant Claims 51-53, 55, 56, 61, 65, and 92 are also obvious in view of claims 81, 99, and 102 for the following reasons.

The method of ligase-mediated recombination of the instant invention is further defined as the hybridization step being repeated, before or after the ligating step (instant claim 51); all of the hybridized (oligonucleotide) fragments having immediately adjacent hybridized oligonucleotide fragments (instant claim 52); polymerase extension filling the gap (or ligating) between the adjacently hybridized oligonucleotide fragments (instant claim 53); method done *in vitro* (instant claim 55); fragments are cleavage fragments (instant claim 56); two heterologous polynucleotide sequences are different from each other at more than one base position (instant

claim 61); two heterologous polynucleotide sequences are single stranded (instant claim 65); and a ligase-mediated recombination (instant claim 92).

Claims 81 of the '316 application renders the above instant claims obvious because claim 81 of the '316 application is drawn to an *in vitro* method (meeting the instant claim 55). The hybridization of the fragments steps being repeated before or after the ligating step (instant claim 51); all of the fragments being hybridized to an assembly matrices (instant claim 52); and ligation of the adjacently hybridized oligonucleotide fragments (instant claim 53) are necessarily conducted and desired when the method of claim 81, which repeats the hybridization and ligation processes. With regard to the cleavage fragments of instant claim 56, claim 81 of the '316 application already requires the use of cleavage fragments. With regard to the two heterologous polynucleotide sequences that are different from each other by at least one base position (or having different sequences), by definition, heterologous polynucleotides are different in their sequences. Further, claim 81 of the '316 application employs polynucleotides that are "different," or differing their sequence by at least one base position. Finally, with regard to the two heterologous polynucleotides being single stranded (instant claim 65), the nature of the invention requires that the polynucleotides be single stranded since oligonucleotides derived therefrom be single stranded to be able to "hybridize" to the assembly matrices. In addition, claim 99 of the '316 application requires that the two different polynucleotides must first be denatured prior to the hybridization step.

Claim 92 which is in an independent form, is met by claim 81 of the '316 application, the differences (the repetition of the method steps) of which have already been discussed above.

Instant claim 54, drawn to the method performed without the use of a polymerase is met by claim 82 of the '316 application.

Instant claim 57 drawn to the fragments being random fragments and instant claim 58 drawn to the method of recombination being random recombination is met by claim 88 of the '316 application, wherein the fragments are produced by random cleavage (therefore, random fragments). The use of random fragments and repetition of the method of instant claim 88 would necessarily produce random recombination products (therefore, random recombination method).

Instant claims 59 and 60, providing fragments that have been obtained in a controlled manner is met by claim 90 of the '316 application, wherein the claim requires that fragments are produced by use of restriction enzyme (thus controlled fragmentation).

Instant claims 66, 67, and 74 drawn to assembly matrix being double stranded but being denatured prior to the hybridization of the oligonucleotide fragments, or being provided in single stranded form, and fragments being used as an assembly matrix is met by claim 98 the '316 application, wherein the oligonucleotide cleavage fragments are used as assembly matrix. Therefore, when the process is repeated, the repetition of the method would necessarily produce a double stranded assembly matrix, followed by denaturation, further followed by ligation. Additionally, the method requires that the assembly matrix hybridize to the oligonucleotide fragments to work, therefore, whether the assembly matrix is first provided in the double stranded form or single stranded is not a patentably distinct sub-step, and clearly obvious in view of the purview of an ordinarily skilled artisan in the discipline of molecular recombination.

Instant claim 68, drawn to thermostable ligase is met by claim 95 of the '316 application.

Instant claim 69, drawn to polynucleotides being artificial in sequence is met by claim 105 of the '316 application.

Instant claim 70, drawn to addition of oligonucleotides varying in length is met by claim 97 of the '316 application.

Instant claim 71, drawn to the bank of polynucleotides being the bank of restricted polynucleotide is met by claim 92 of the '316 application

With regard to instant claim 72, wherein the produced recombinant polynucleotide being novel, such is an obvious characteristic of the method, and is not a patentably distinct limitation.

Instant claim 73 and 87, drawn to cloning the recombinant polynucleotide sequence is met by claim 101 of the '316 application. The cloning of the recombinant polynucleotide would also render the *in vitro* expression of the recombinant polynucleotide sequence because the nature of the method is to produce a recombinant polynucleotide and clone such a sequence to express a polypeptide (thus *in vitro* expression) for the purpose of determine whether or not the recombinant product exhibits an advantageous characteristic over the wild-type product.

Instant claims 75 and 76, drawn to subjecting the polynucleotide sequences to hydrolysis by use of a restriction enzyme having a plurality of different cutting sites or a plurality of restriction enzymes, is met by claims 91 and 92 of the '316 application.

Instant claims 77 and 78, drawn to random fragmentation of the polynucleotide sequences and employing them as assembly matrix is met by claims 89 and 90 of the '316 application.

Instant claim 79, drawn to hybridization and ligation steps being performed simultaneously is met by claim 86 of the '316 application.

Instant claim 81, drawn to selecting a recombinant polynucleotide sequence having advantageous characteristics and using said recombinant polynucleotide sequence is met by claim 85.

Instant claims 82 and 86, drawn to choosing one recombinant polynucleotide sequence as a source of fragments or as an assembly matrix is met by claim 100 of the '316 application.

Instant claims 83 and 84, drawn to separating the recombinant polynucleotide and the method in which it is separated is met by claim 101 of the '316 application because when a polynucleotide is cloned, such polynucleotide must first be isolated, wherein the isolation contemplated by the specification disclose the marker assisted isolation as the choice method (see page 10, lines 24-33, the '316 application).

Instant claim 85, drawn to the use of polymerase extension to amplify the number of recombinant polynucleotide is met by claim 83 of the '316 application.

Instant claim 88, drawn to the use of a degrading enzyme to degrade non-hybridized ends of the fragments is met by claim 93 of the '316 application.

Instant claim 89, drawn to the degrading enzyme being Flap endonuclease is met by claim 94 of the '316 application.

Instant claim 90, drawn to the degrading enzyme and ligase being equally thermostable is met by claim 96 of the '316 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 62-64 and 91 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 81 and 93 of copending Application No. 09/723,316 in view of Katsumata et al. (U.S. Patent No. 4,500,640, issued February 19, 1985) and Stemmer et al. (U.S. Patent No. 5,830,721, issued November 3, 1998).

Instant claims 62-64 are drawn to the two heterologous polynucleotide sequences being derived from different genes (claim 62), distinct gene families (claim 63), different species (claim 64).

Instant claim 91 is drawn to the use of degrading enzyme to degrade non-hybridized ends of the fragments by use of an exonuclease.

Stemmer et al. disclose a method of generating random recombinant polynucleotides (column 4, lines 6-21). Stemmer et al. disclose that the polynucleotides from variety of sources could be employed in the generation of random recombinant polynucleotides, such as related genes from single species or related genes from different species.

Katsumata et al. disclose a well-known activity of an exonuclease, wherein the activity involves the cleaving of single stranded nucleic acids (column 5, lines 61-65).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teachings of Stemmer et al. and Katsumata et al. to arrive at the invention as claimed for the motivation discussed below.

Stemmer et al. disclose that while their example shuffled a single gene through the method, the diversity present in the mixture (of fragments that become recombined) would be more meaningful than the random mutations that are generated, wherein the artisans give an example of using related genes from a related species or many different species for

recombination process (column 48, lines 50-60), thereby reasonably motivating the ordinarily skilled artisan at the time the invention was made to use the polynucleotides of different genes, gene families, and different species.

With regard to the use of exonuclease for the purpose of cleaving single stranded nucleic acids, one of ordinary skill in the art at the time the invention was made would have recognized that an exonuclease would have been useful in cleaving single stranded nucleic acids, as evidenced by Katsumata et al. Since claim 93 of the '316 application already contemplates cleaving a single stranded nucleic acid in their method, one of ordinary skill in the art would have had a reasonable expectation of success at using an exonuclease for the same purpose with a reasonable expectation of success.

Therefore, the invention as claimed is obvious over the cited references.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (517) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Young J. Kim
Patent Examiner
Art Unit 1637
2/26/04

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
3/1/04